IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Application of
Karl Kolter et al.
Serial No.09 /811,546
Filed: March 20, 2001
For: Solid oral dosage forms with delayed release of active ingredient and high mechanical stability

DECLARATION

I, Karl Kolter, Dr. rer. Nat., a citizen of Germany and a resident of Sudetenstrasse 1, 67117 Limburgerhof, Germany, hereby declare and say as follows:

I am a fully trained pharmacist, having studied pharmacy at Mainz University in the period of from 1976 to 1981.

I was awarded my PhD in Mainz, where in the period of from 1981 to 1985 I worked as an assistant at Mainz University.

I joined Knoll AG, a former subsidiary of BASF Aktiengesellschaft, located in 67061 Ludwigshafen, in 1986 , where I have been engaged in research and development in the field of pharmaceutical formulations.

In 1993 I joined BASF Aktiengesellschaft, now named BASF SE, and I have since been engaged in the field of development of pharmaceutical excipients and formulations of active ingredients.

I am a co-inventor to Application Serial No. 09 /811,546;

I have carefully studied the final Office Action of September 17, 2009 and the rejection of the claims under 35 U.S.C. §112, 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a).

Now, hereby, I want to state the following:

In the Office Action of September 17, 2009 it was contended that the allegation of unexpected results is not commensurate with the scope of the claims since results showing a synergistic effect were only demonstrated for hydroxypropylmethylcellulose.

In order to demonstrate that the synergistic effect is not limited to a combination of the formulated mixture of polyvinyl acetate and polyvinyl pyrrolidone, Kollidon SR, with water-soluble swelling polymers like HPMC I want to submit additional comparative date regarding the use of a lipophilic substance like stearic acid and Kollicoat MAE as a water-insoluble polymer.

Combination Kollidon SR / Stearic Acid

The tableting mixtures were prepared as described in the respective examples of the present application. In Example 5 the release slowing effect of a small amount of stearic acid had already been demonstrated for Batch L (Tables 7 and 8). In order to show that the same amount of stearic acid alone does not have positive effects and that the effect is synergistic, the results for stearic acid alone (Comparative Ex. I) are compared to the results for Batch A, which is also a comparative example)

Batch	A (Comp.)	L	Comp. Ex. I [mg]
Koffein gran. 02/05	160	160	160
Kollidon SR	160	160	-
Stearic Acid	-	40	40

	Spec., Table 9 A	Spec. , Table 9 L	Comp. Ex. I
Hardness [N]	295	274	50
Friability [%]	0.01	0.02	1.53

This clearly demonstrates that stearic acid alone offers no positive effect. The tablets according to Comparative Example I are insufficient with regard to hardness and friability.

Active ingredient Release [%]

	Spec. , P. 16 Table 10	Spec. , P. 16 Table 10	Comp. Exp.	
Time [h]	Caffeine 160 mg Kollidon SR 160 mg	Caffeine 160 mg Kollidon SR 160 mg Stearic Acid 40 mg	Caffeine 160 mg Stearic Acid 40 mg	Caffeine 160 mg Kollidon SR 200
0	0	0	0	0
0,5	10,9	7,3	29,5	10,1
1	16,9	11,5	45,8	15,9
1,5	20,7	14,8	56,5	19,5
2	24,4	17,2	64,0	23,0
3	29,7	21,8	73,9	28,2
4	33,9	24,7	87,6	32,3
6	40,3	30,0	94,5	38,8
8	46,1	34,4	94,1	44,0
12	55,8	43,4	96,5	53,2
16	64,4	49,7	99,0	61,1

The addition of a small amount of stearic acid significantly slows the release of the active ingredient whereas the same amount of stearic acid alone does not have such effect. Also, the release slowing effect is not caused simply by the amount of release slowing excipient.

This becomes very clear from the release curves as depicted in the attachment to this Declaration. It is evident that the combination of 40 mg stearic acid and 160 mg Kollidon SR, (total amount of release slowing combination 200 mg), shows a significantly stronger release slowing effect than 200 mg of Kollidon SR alone.

Combination Kollidon SR/ Kollicoat MAE

Furthermore, I want to submit the following addition data (Comparative Example II) relating to the combination with Kollicoat MAE in order to show that this combination as well shows a synergistic effect.

In Example 6 it was already demonstrated that the combination of Kollidon SR with small amounts of the acrylic copolymer Kollicoat MAE shows positive effects with regard to slowing of release and mechanical properties of the tablets. The same amount of Kollicoat MAE alone (Comp. Ex. II)

	Ex. 6, Table 11 [mg]		Comp. Ex. II [mg]
	Batch M	Batch N	
Propranolol HCl	160	160	160
Kollidon SR	160	160	-
Kollicoat MAE 100 P	-	40	40

	Table 11 M	Table 11 N	Comp. Ex. II
Hardness [N]	216	271	43
Friability [%]	0.02	0.02	8.97 capping

This clearly demonstrates that Kollicoat MAE alone offers no positive effect with regard to tablet hardness and friability. The tablets according to the comparative example are not only insufficient with regard to hardness and totally unsatisfying with regard to friability, but also have a strong tendency to capping, an unwanted phenomenon in tablet production.

Active Ingredient Release [%]

	Ex. 6, Table 12 Batch M	Ex. 6, Table 12 Batch N	Comp. Ex. II
time[h]	Propranolol HCl 160 mg Kollidon SR 160 mg	Propranolol HCl 160 mg Kollidon SR 160 mg Kollicoat MAE 40 mg	Propranolol HCl 160 mg Kollicoat MAE 40 mg
0	0	0	0
0,5	19,4	10,0	87,9
1	25,3	15,5	98,6
1,5	31,8	18,9	97,0
2	38,0	22,4	100,0
2,5	41,5	24,6	-
3	45,8	26,5	-
4	53,9	30,6	-
5	59,7	33,4	-
6	64,2	34,7	-
7	68,9	36,6	-
8	71,8	38,2	-
9	74,8	40,4	-
10	77,3	41,7	-
11	79,4	43,7	-
12	81,8	45,4	-
16	86,3	51,7	-

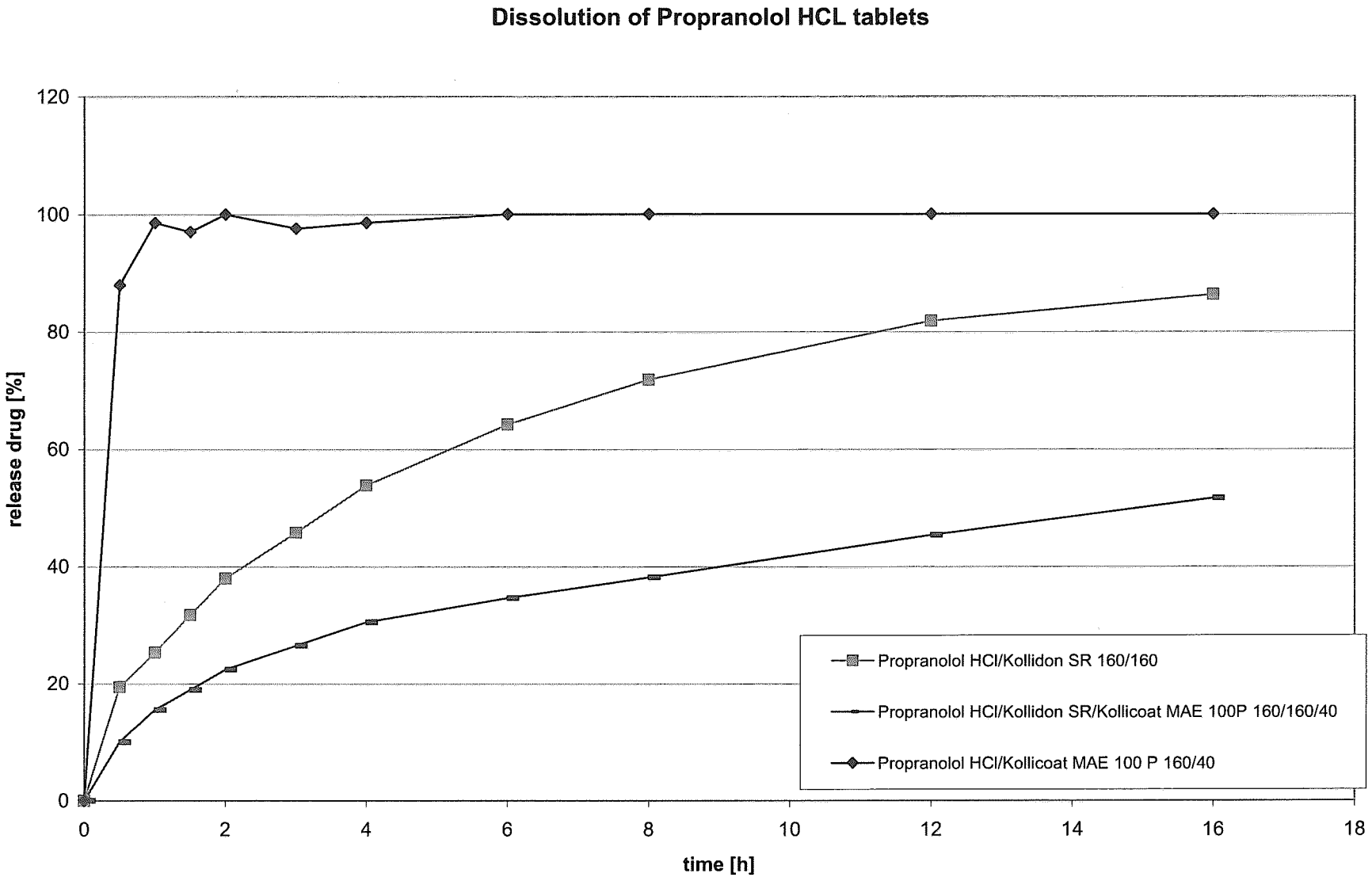
The addition of a small amount of Kollicoat MAE distinctly reduces the release of the active ingredient. The same amount of Kollicoat MAE alone does not show a significant release slowing effect. The attached drawing depicting the release curves clearly demonstrates the synergistic effect.

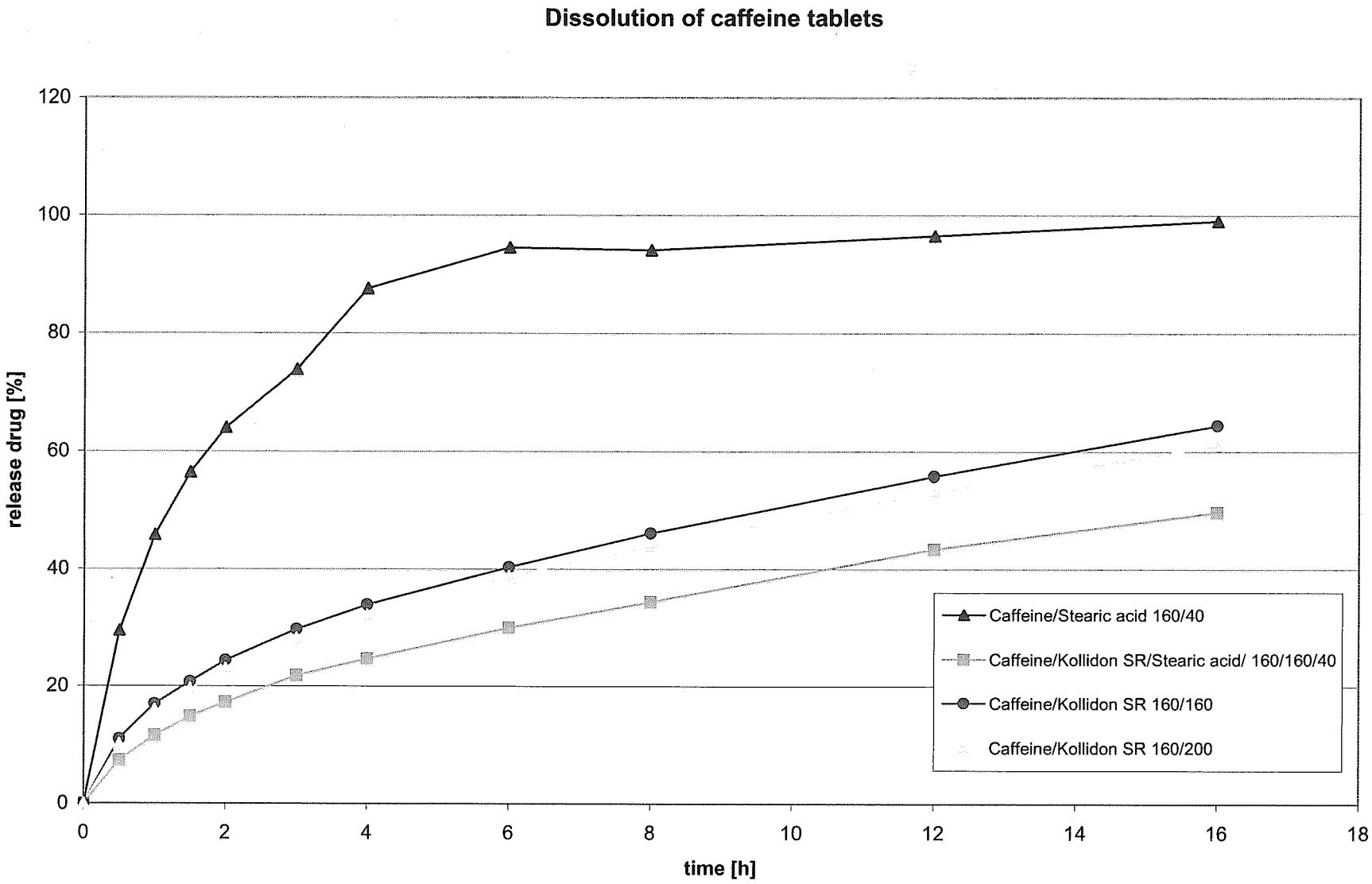
I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so are made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at 67056 Ludwigshafen, Germany, this 24th day of March 2010.

Signature of Declarant

Attachment : 2 Drawings (Dissolution of Propanolol HCl tablets; Dissolution of caffeine tablets)


Dissolution of Propranolol HCL tablets
120
100
80
60
40
20
0
release drug [%]
0
2
4
6
8
10
12
14
16
18
time [h]
Propranolol HCl/Kollidon SR 160/160
Propranolol HCl/Kollidon SR/Kollicoat MAE 100P 160/160/40
Propranolol HCl/Kollicoat MAE 100 P 160/40


Dissolution of caffeine tablets
120
100
80
60
40
20
0
release drug [%]
0
2
4
6
8
10
12
14
16
18
time [h]
Caffeine/Stearic acid 160/40
Caffeine/Kollidon SR/Stearic acid/ 160/160/40
Caffeine/Kollidon SR 160/160
Caffeine/Kollidon SR 160/200